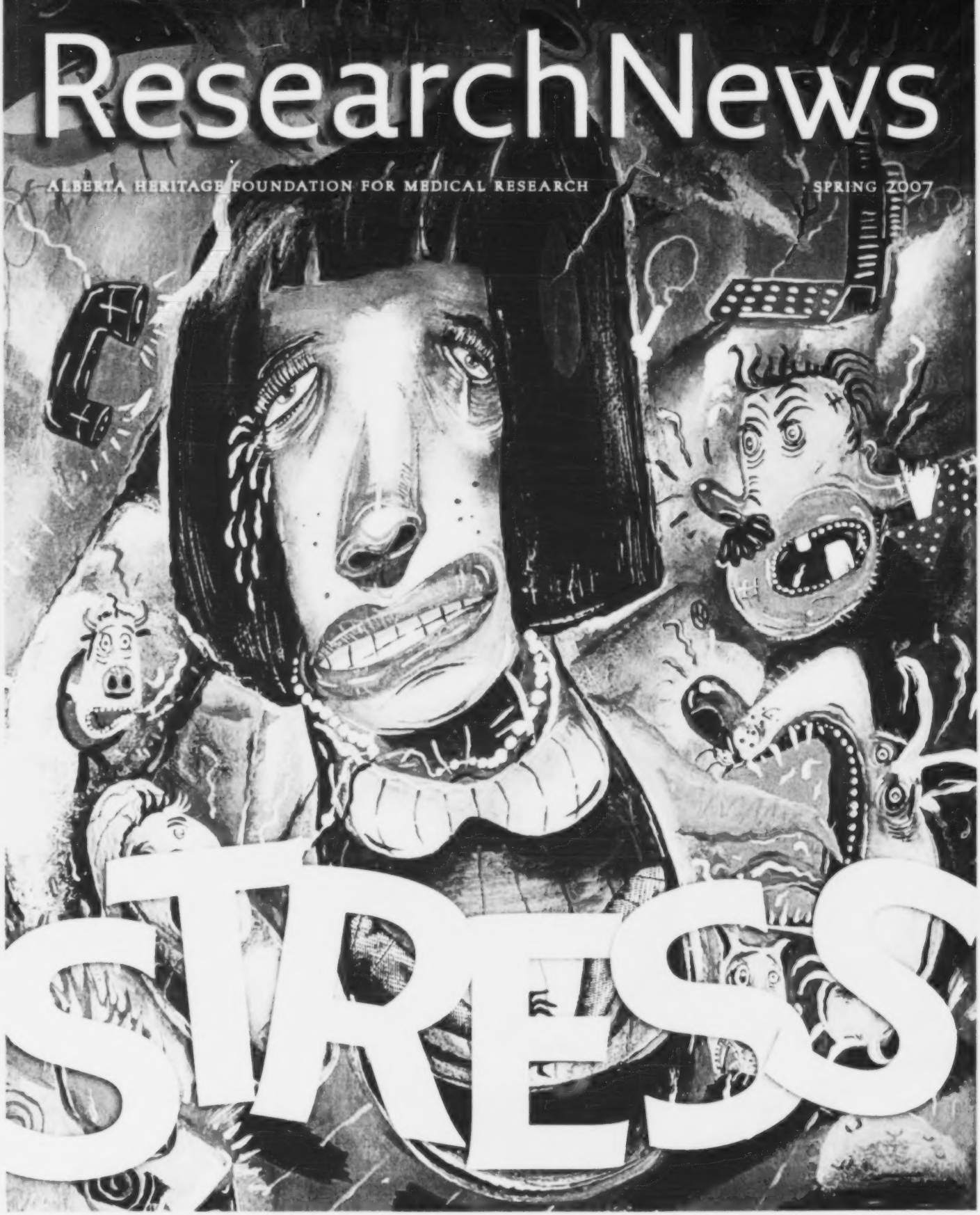
REGROWING TEETH | GENES AND NUTRITION | BLOOD FLOW AND THE BRAIN

ResearchNews

ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

SPRING 2007



STRESS

On the cover

Rick Sealock was born and raised in the wild wilds of southern Alberta in the 60s where he won many blue ribbons for his wild art class drawings and running/jumping events. After graduating from the even more wild Alberta College of Art & Design, Rick became a freelance illustrator. He has received more than 250 wild illustration awards and worked with such clients as the *Los Angeles Times*, *Rolling Stone*, *Time*, Walt Disney, and the *Washington Post*. He recently moved from Calgary to Kitchener, Ontario with his wife, his newborn daughter, and three cats, all living in one small wild house.

AHFMR MISSION

AHFMR supports a community of researchers who generate knowledge, the application of which improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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AHFMR
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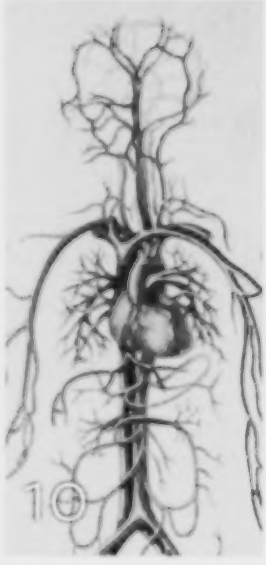

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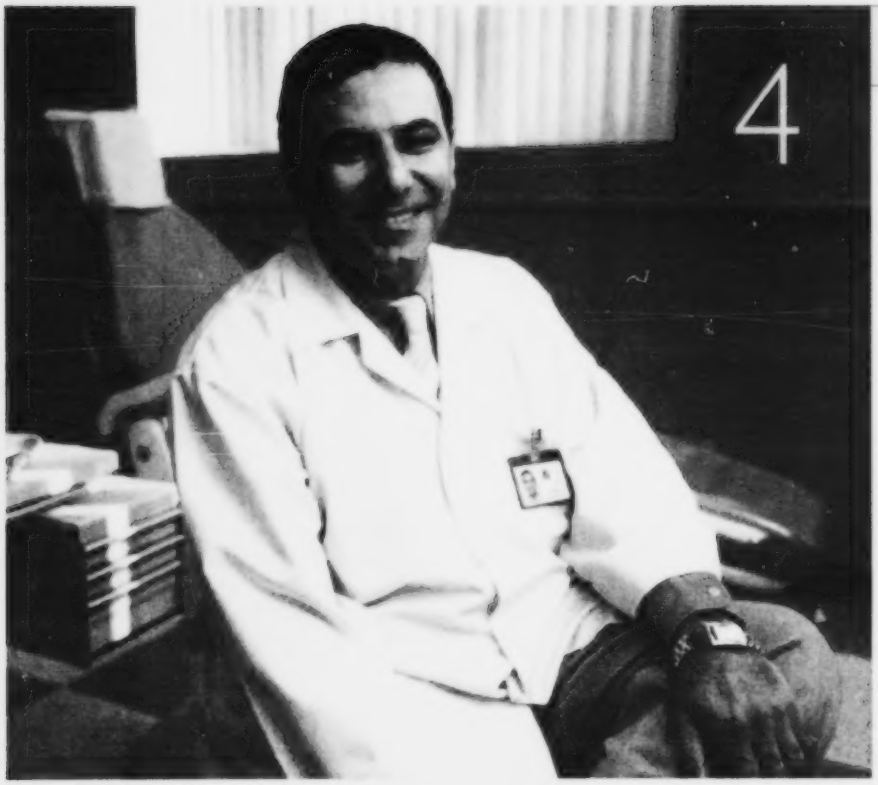

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You are what you eat

From designer diets to disease treatment, nutrigenomics may make us look at food in a whole new way. Dr. David Castle explains.

"LET FOOD BE YOUR MEDICINE AND YOUR MEDICINE BE FOOD." These words from the ancient Greek physician Hippocrates are taking on new meaning today. Until now, dietary recommendations (for example, that everyone should eat less fat) have been based on a one-size-fits-all approach. In future, however, thanks to increased knowledge of genetics and availability of genetic testing, it may be possible to develop "designer diets"—diets tailored to an individual's genetic make-up that will reduce risk factors for certain diseases.

THIS FLEDGLING SCIENCE is called *nutrigenomics*: the study of the interaction between genes and nutrition. It is one of the major interests of Dr. David Castle, Canada Research Chair in Science and Society and co-author of *Science, Society, and the Supermarket*, the first book on nutrigenomics.

"Nutrigenomics is one of the first tangible results of the Human Genome Project, the 13-year project that identified and sequenced all the genes in human DNA," says Dr. Castle. "Researchers are taking this information about genes and investigating the roles nutrients play."

> In future, it may be possible to develop "designer diets"

By way of example, Dr. Castle points to recent studies suggesting that high blood levels of an amino acid called homocysteine put people at elevated risk for heart disease. Folic acid, which is present in leafy green vegetables, helps break down homocysteine in the body, but some people have gene variations that make it difficult for their bodies to use folic acid. One recommendation might be for these people to consume higher doses of folic acid; although they wouldn't be able to metabolize it very well, increasing the amounts would increase the benefit.

"While there are still questions about the science behind nutrigenomics, there is good evidence that some nutrients can play an active role in metabolism, just as drugs do. Researchers are also discovering that nutrient-gene associations have a role to play in reducing your relative risk for certain diseases, and that by modifying your diet you can reduce your risk. People sometimes overextend the claims for nutrigenomics and talk about nutrigenomics in terms of treating disease; however, there is currently no clinical work that demonstrates disease treatment."

Dr. Castle points out that nutrigenomics is already being offered directly to consumers. A number of companies (mainly in the United States) offer testing services. A customer sends in a DNA sample, taken by a brush swab on the inside of the cheek, and—for a fee—the company tests for variants of several genes that might indicate risk for certain diseases or physiological imbalances. The company provides dietary recommendations based on the test results.

> "Nutrigenomics is one of the first tangible results of the Human Genome Project"

"The downside of nutrigenomics going direct to consumers is the extreme shortage of healthcare professionals who can help consumers interpret the results of nutrigenomics testing. Few primary-care practitioners know much about nutrition, except for those in a dietetics practice, and very few know much about genetics. An even smaller subset know about both nutrition *and* genetics. This is going to be a difficult hurdle to overcome.

"I think it is inevitable that, as we learn more about how nutrients impact gene expression we're going to realize that the bioactivity of some nutrients is as great as, if not greater than, [the activity of] some pharmaceutical components. The growth of the science will pose some interesting questions for the regulation of foods and drugs and the impact on the safety of patients and consumers. I'm looking forward to how this will unfold." ❋

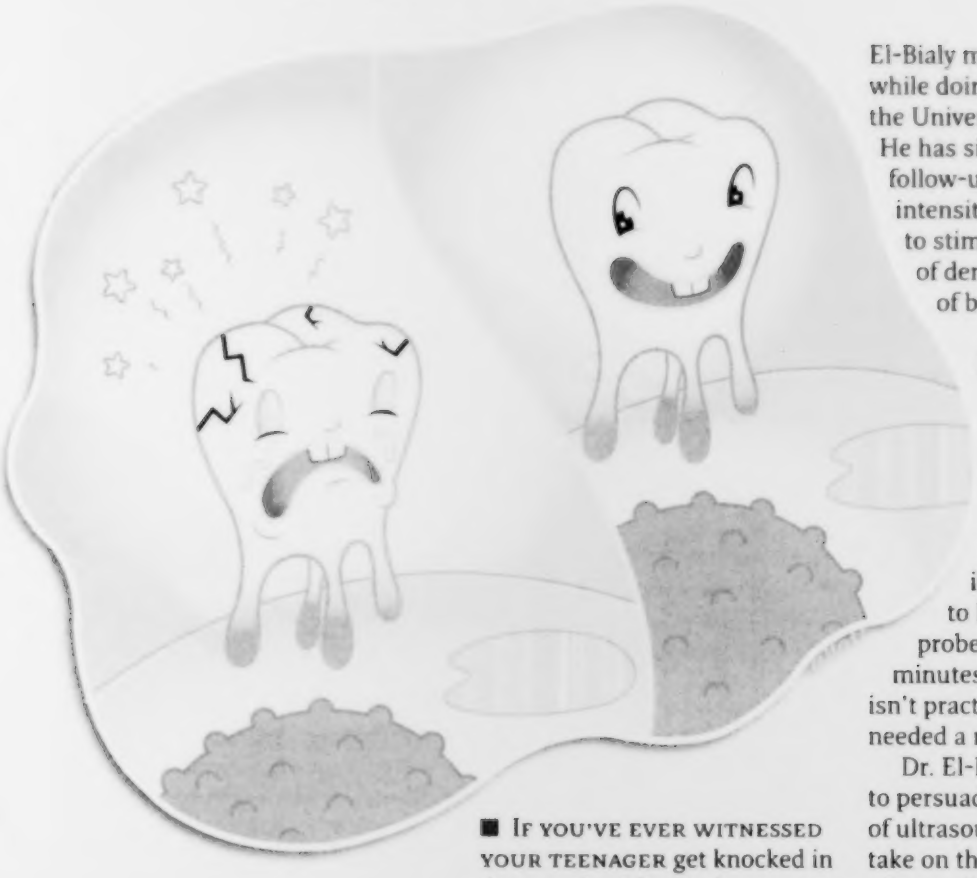
Dr. David Castle is Canada Research Chair in Science and Society and a philosophy professor at the University of Ottawa. He studies the cultural, social, and ethical issues raised by science and technology and their ramifications for Canadian domestic and foreign policy.

Recommended reading

Castle D, Cline C, Daar AS, Tsamis C, Singer PA. *Science, Society, and the Supermarket: The Opportunities and Challenges of Nutrigenomics*. Hoboken (NJ): Wiley-Interscience; 2007.

Cutting teeth

Dr. Tarek El-Bialy and other University of Alberta researchers have developed a tiny ultrasound device that may help regrow damaged teeth.



■ IF YOU'VE EVER WITNESSED YOUR TEENAGER get knocked in the mouth while playing sports, or if you've taken a hit to your own teeth, you know that sinking feeling. While all sorts of other injuries can heal, you can't grow a new tooth. At least that's what we *thought*.

A researcher from the University of Alberta has found that a type of ultrasound can help regrow dental tissue. Dr. Tarek El-Bialy made the discovery while doing his Ph.D. at the University of Illinois. He has since conducted follow-up studies using low-intensity pulsed ultrasound to stimulate both the healing of dental tissue and growth of bone in the jaw.

"We have compelling evidence from research that the technology works; however, the equipment is large and unwieldy," says Dr. El-Bialy. "In our clinical trials, people had to hold an ultrasound probe in their mouth for 20 minutes each day. This just isn't practical. It was clear we needed a much smaller device."

Dr. El-Bialy tried in vain to persuade manufacturers of ultrasound equipment to take on the project. Then a bit of serendipity came into play. When Dr. El-Bialy joined the University of Alberta in 2005, he attended the orientation program for new staff. One of the presenters was Dr. Jie Chen from the university's Faculty of Engineering and the National Institute for Nanotechnology. Dr. Chen spoke about teaching methods in microfabrication

About Forefront

AHFMR's ForeFront programs work to apply health research into innovative products and services that lead to improved health. For more information go to *http://www.ahfmr.ab.ca/forefront*

and nanotechnology (the field of study that creates devices on an extremely small scale—the level of atoms and molecules). "I knew immediately that this was the guy I was looking for," says Dr. El-Bialy.

The result was a collaboration between Dr. El-Bialy, Dr. Chen, and Dr. Ying Tsui, also from the Faculty of Engineering. The team received an Idea to Innovation (I2I) grant from NSERC (the Natural Sciences and Engineering Research Council) to miniaturize the technology. Now the size of a fingernail, the device slips over a tooth, fitting comfortably in the mouth. Inside the device, a tiny battery-powered transmitter beams ultrasound waves to the root of the affected tooth.

Dr. El-Bialy has secured Phase 1 funding from AHFMR's ForeFront program for testing the transmitter in animals. ForeFront's integrated programs support scientists in translating the results of their research into innovative products and services that lead to improved health. "ForeFront funding has really helped move technology development along," notes Dr. El-Bialy. "Hopefully by the summer we'll have the results from our tests. We're also applying to Health Canada for approval for a clinical trial on humans."

The device slips over a tooth

One of the major applications of this little ultrasound transmitter is in treating dental root resorption—the breakdown and eventual loss of a tooth's root structure. Orthodontic braces can cause progressive root resorption, limiting the length of time braces can be worn. The ultrasound device could counteract this destructive process. It can also be used to heal root fractures, to regrow dental pulp in root canals, and to treat periodontal disease.

How best to commercialize this technology is yet to be decided. Meanwhile TEC Edmonton (a joint venture between the University of Alberta and the Edmonton Economic Development Corporation) is helping to protect the intellectual property and market the technology. The first patent has been filed in the US.

"I didn't set out to be an entrepreneur," says Dr. El-Bialy. "My mission was to try to solve a problem—tooth-root resorption. But when I found that companies weren't interested in doing the necessary R & D, I had to find a way to do it myself. Alberta has been a good place to take on this project." ✲

Winning technology

The intra-oral ultrasound device for tooth healing (pictured here) developed by University of Alberta researchers won the $1,000 first prize at TechMed Alberta in March 2007. The AHFMR-sponsored prize is awarded for visual presentation, research content, and commercial opportunity. WestLink Innovation Network, which stages TechMed, bills the event as "Canada's marketplace for emerging medical technologies". The annual, multi-city event showcases recent innovative technologies and research to show industry the partnering and licensing opportunities available in Western Canada.

About the researcher

Dr. Tarek El-Bialy is an associate professor in the Faculty of Medicine and Dentistry at the University of Alberta.

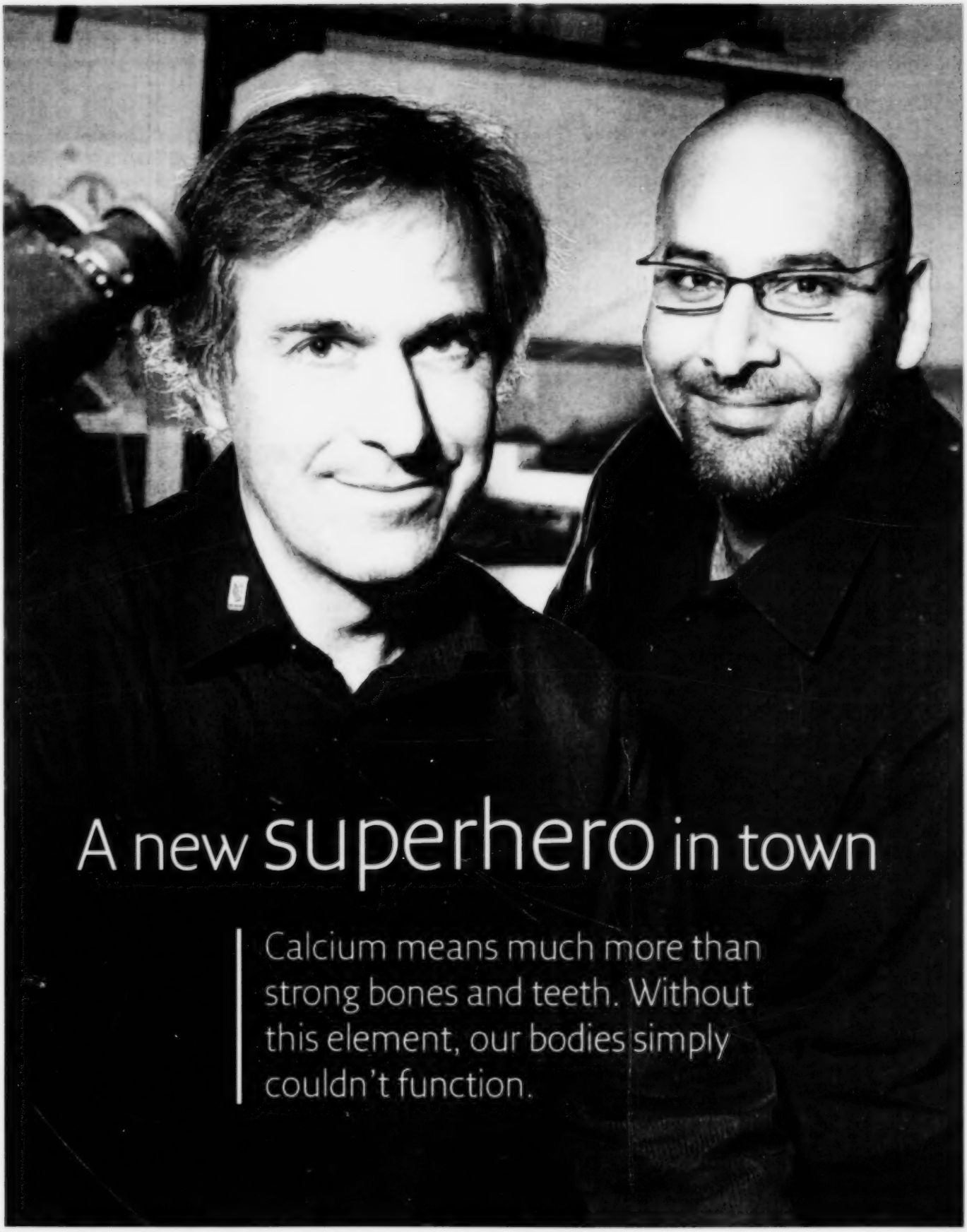
Selected publication

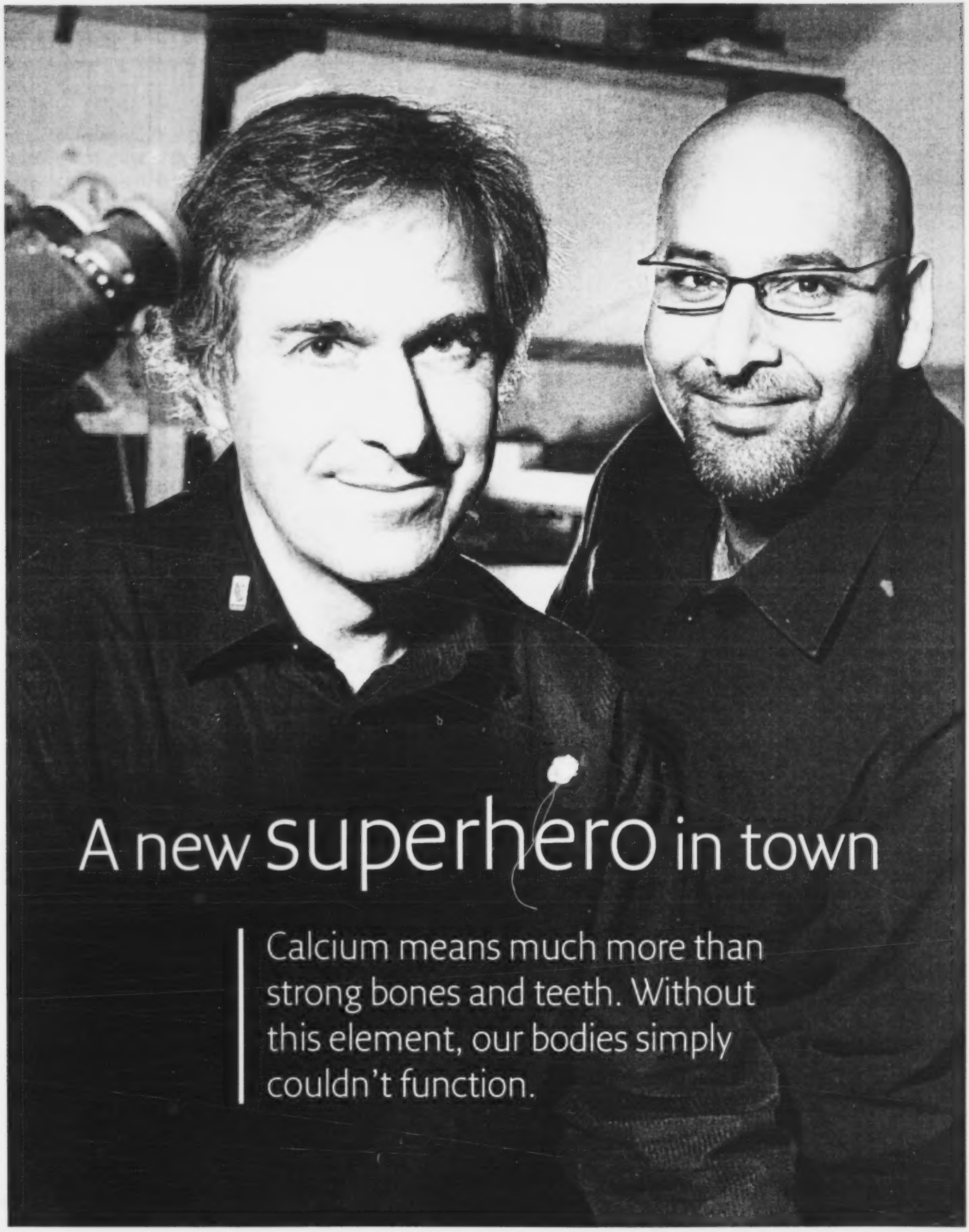
El-Bialy T, El-Shamy I, Graber TM. Repair of orthodontically induced root resorption by ultrasound in humans. *American Journal of Orthodontics and Dentofacial Orthopedics* 2004 Aug;126(2):186-193.

Recommended website

Ultrasonic Dental Modification Device website

http://www.ece.ualberta.ca/~jchen/Old-Dreamweaver/dental.html


A new superhero in town
Calcium means much more than strong bones and teeth. Without this element, our bodies simply couldn't function.



A new superhero in town

Calcium means much more than strong bones and teeth. Without this element, our bodies simply couldn't function.

Dr. Jonathan Lytton (L) and Dr. Jaideep Bains

There's a new superhero in town. But this one isn't a fictional character with superhuman powers. This superhero is the common, everyday element known as calcium—the fifth-most-abundant element in the Earth's crust.

OFTEN, WHEN WE THINK OF CALCIUM, WE THINK OF STRONG BONES AND TEETH. Many of us might think of dietary calcium, and ask ourselves whether we get enough milk, almonds, and other calcium-rich foods in our daily food regimen. Some might even think of concrete buildings and sidewalks, as calcium from limestone is an important ingredient in the kind of cement used for concrete. Still others might know about the part that calcium plays in manufacturing rocket propellant, fireworks, paints, fertilizer, deodorant, and metal alloys.

VERY MUCH OUT OF THE PUBLIC EYE, however, is calcium's essential role in *signalling* (triggering) many body functions. Nerve impulses, heart rhythm, muscle contractions, even cell division, are all regulated by the transport of calcium into and out of cells. A signalling superhero, calcium has a functional role common to all living organisms.

AHFMR has supported Dr. Jonathan Lytton's study of calcium since 1995, when he returned to the University of Calgary from Brigham and Women's Hospital, affiliated with Harvard Medical School. The Heritage Scientist explains why calcium is so important: "Without calcium, our muscles wouldn't contract, our hearts wouldn't beat, our brains wouldn't work, our immune cells wouldn't respond to infection—the list goes on and on. Calcium is needed from the moment of fertilization that creates a new life, to the moment of death."

AND HOW DO CELLS DEAL WITH ALL THIS CALCIUM? A family of proteins on the surface of cells plays a part in its transport. These proteins, known as sodium/calcium exchangers (Na^+/Ca^{2+} exchangers), are vital to a cell's ability to properly handle calcium. Dr. Lytton studies the transport of calcium into and out of cells, particularly the role played by this protein family. The presence and proper functioning of these exchangers ensure that just the right amount of calcium is received at just the right time. When the system controlling calcium works, changes in calcium levels occur in a cyclical fashion, signalling the beginning and end of a heartbeat, or the beginning and end of a signal between two neurons. But when the system fails

Dr. Jonathan Lytton (L) and Dr. Jaideep Bains

Move over, Superman! There's a new superhero in town. But this one isn't a fictional character with superhuman powers. This superhero is the common, everyday element known as calcium—the fifth-most-abundant element in the Earth's crust.

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THE ROLE OF CALCIUM

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> Calcium has a functional role common to all living organisms

> When the system fails, damage can result

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CALCIUM IN THE CELL

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Quick Facts

More on calcium...

Calcium is the most plentiful mineral in the human body. More than 99% of the body's calcium is found in the bones and teeth where it serves to support their structure. The other 1% is found in blood, muscle, and the fluid between cells. Calcium is required for the body to contract muscles, expand and contract blood vessels, secrete hormones and enzymes, and send messages through the nervous system.

Source: National Institutes of Health (Office of Dietary Supplements)

or becomes impaired, damage can result—in the form of cardiac arrhythmia, heart failure, stroke, or dementia.

Dr. Lytton uses the techniques of molecular biology, genetic engineering, biochemistry, cell biology, and physiology in his efforts to understand how sodium/calcium exchangers work, how their function is regulated under normal conditions, and what happens when their function is impaired. Although his work is mostly concerned with fundamental principles and mechanisms, a detailed understanding of how these proteins work will provide a foundation of new knowledge, from which it will be possible to develop important new clinical, diagnostic, and therapeutic tools.

COLLABORATIONS

Some of Dr. Lytton's discoveries have led his work down new and unexpected pathways, often requiring the development of new experimental approaches and new equipment. Such innovations do not happen in isolation. The highly collaborative environment at the University of Calgary has presented many opportunities. In particular, the collaboration of AHFMR researchers Dr. Ray Turner, Dr. Jaideep Bains (see *Stress* story on page 12), and Dr. Derrick Rancourt, as well as trainees and researchers at the doctoral and post-doctoral levels, has greatly benefited Dr. Lytton's research. "Having excellent collaborators has allowed my lab to make rapid progress, which would have been much more difficult, if not impossible, in other environments," says Dr. Lytton.

Soon, with the help of AHFMR, Dr. Lytton's research will advance further,thanks to the arrival of a customized $90,000 Zeiss Axioskop (see *Cool tools* story on page 9)—the best equipment of its kind—to help reveal the secrets of calcium's superpowers. Once this microscope is in place, only one more ingredient will be needed before Dr. Lytton and his team can start to unlock these molecular mysteries: a highly skilled electrophysiologist to operate the Axioskop.

With a strong supporting cast of researchers and collaborators, plus a lab equipped with specialized tools, Dr. Lytton's study of calcium transport is well positioned to make extraordinary leaps and bounds into the future. ❋

About the researcher

Dr. Jonathan Lytton is an *AHFMR Scientist* and a full professor in the Department of Biochemistry and Molecular Biology at the University of Calgary.

Selected publication

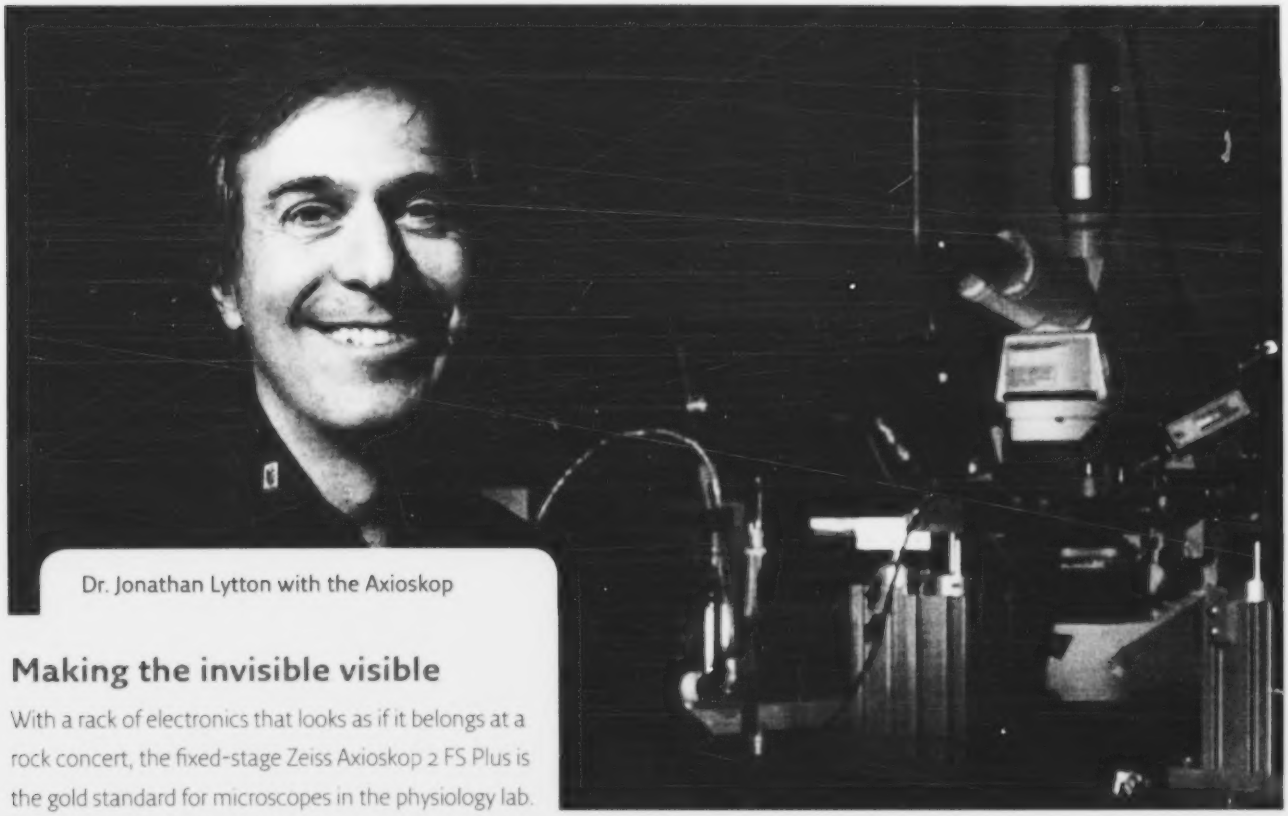
Li X-F, Kiedrowski L, Tremblay F, Fernandez FR, Perizzolo M, Winkfein RJ, Turner RW, Bains JS, Rancourt DE, Lytton J. Importance of K^+-dependent Na^+/Ca^{2+}-exchanger 2, NCKX2, in motor learning and memory. *Journal of Biological Chemistry* 2006 Mar 10;281(10):6273-6282.

Recommended website

National Institutes of Health (Office of Dietary Supplements) Fact Sheet: Calcium

http://dietary-supplements.info.nih.gov/factsheets/calcium.asp

Cool tools



Dr. Jonathan Lytton with the Axioskop

Making the invisible visible

With a rack of electronics that looks as if it belongs at a rock concert, the fixed-stage Zeiss Axioskop 2 FS Plus is the gold standard for microscopes in the physiology lab. This small miracle of modern technology is used in the life sciences to examine minute parts of living specimens, such as wafer-thin layers of live nerve-cell tissue. Such live investigations are possible thanks to a temperature-controlled chamber and optical objectives (the "eyepieces" of the microscope that house the lenses) that can be immersed in a saltwater solution.

Once under the microscope's lenses, specimens can be illuminated by different methods to provide the best possible viewing. For example, the Axioskop allows scientists to use fluorescent dyes to help them observe cellular activity. When fluorescence is used, the Axioskop must be housed in a room that can be completely darkened—something akin to a photographer's darkroom. A super-sensitive camera detects the fluorescence and sends images to a computer monitor. The Axioskop can also illuminate specimens using light in the infrared range.

Researchers may customize their Axioskops with many accessories. Micromanipulators—small, delicate "arms" that can hold electrodes to measure the electrical activity in cells or wield instruments to carry out tasks too complex for the naked eye. A motorized stage, operated by means of a joystick, facilitates seamless and vibration-free examination of an entire specimen. A special copper screen surrounds the Axioskop to block electrical interference. The Axioskop may even come equipped with a laser capable of breaking open chemical bonds, useful for isolating certain chemicals under investigation.

The most important add-on to a Zeiss Axioskop, however, is the highly skilled technician required to make it work. Graduate students or post-doctoral electrophysiologists are in high demand as operators of this type of equipment. ❋

Blood flow, aging, and the brain

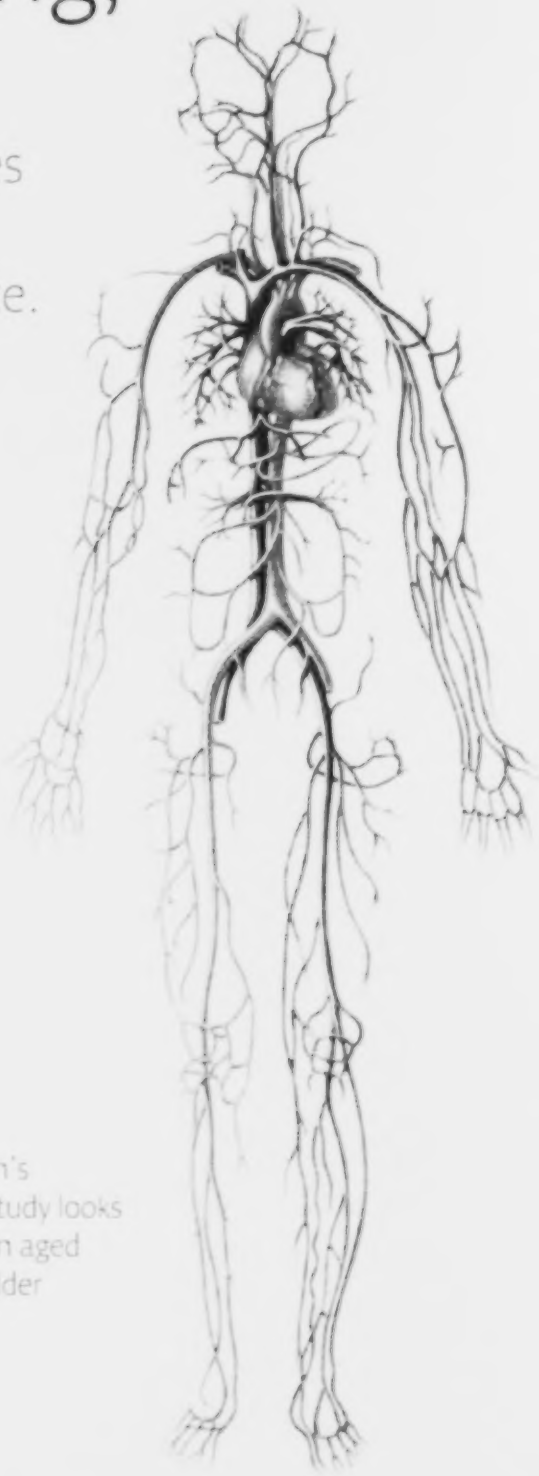
Blood flow in the brain changes as we age, a fact which may affect our risk of having a stroke.

Interrupt the flow of blood to any part of the brain, and the result can be a devastating stroke. Although the brain makes up only about 2% of the total body weight in humans, it receives 15% to 20% of the body's blood supply. Brain cells die if the supply of oxygen-carrying blood stops. Accordingly, the brain is exquisitely sensitive to changes in the levels of carbon dioxide and oxygen in the blood, and can quickly regulate blood flow to maintain oxygen delivery.

■ Heritage Senior Scholar Dr. Marc Poulin from the University of Calgary has a window on blood flow in the brain. He uses advanced Doppler ultrasound equipment—one of only two such set-ups in the world—to better understand diseases such as stroke. This powerful technology can analyze blood flow 100 times per second and average all the data within the time it takes for a single heartbeat.

Dr. Poulin's ultrasound studies cover many different areas, one of which is how blood flow in the brain changes with age in women and how this might affect their risk of stroke. Women are the faster-growing group of the senior population; since stroke rates in women double during each decade of life after the age of 55, the number of strokes in females will rise substantially over the next 15 years.

Dr. Poulin's current study looks at women aged 50 and older



Quick Facts

- **Stroke** is the number *one cause of major* disability in adults and the number three cause of death in the United States and Canada.
- **Stroke** is caused by the interruption of flow of blood to the brain (*ischemic stroke*) or the rupture of blood vessels in the brain (*hemorrhagic stroke*).
- The longer the brain goes without the oxygen and nutrients supplied by the blood flow, the greater the risk of permanent brain damage.

BLOOD SUPPLY AND STROKE

DR. POULIN'S CURRENT STUDY looks at women aged 50 and older, and includes both physically fit and sedentary individuals. "We're looking to see how age affects the brain's ability to increase blood supply when challenged," explains Dr. Poulin. "We're hypothesizing that exercise boosts the brain's ability to do this. We're also doing cognitive-function tests on these women, and are hoping to relate cognitive function to cerebral blood flow. If these hypotheses show promise, we'll follow up with a larger study."

> The brain receives 15% to 20% of the body's blood supply

In addition to providing a better understanding of the mechanisms that control cerebral blood flow, this research has potential applications for stroke prevention. A stroke occurs when the blood supply to the brain stops; so the reduced ability to increase blood supply may make the brain particularly susceptible to stroke. One possible outcome of Dr. Poulin's research could be the development of a non-invasive test to identify susceptible individuals.

"I started off as a basic researcher, but over time I've become more and more interested in applying the knowledge from the lab to improve health care. Stroke is a very serious challenge. Circulatory diseases, including stroke, are the number one cause of major disability and death in adults in Canada; and the annual national cost of stroke is almost $3 billion. I'm hoping that my work will facilitate better assessment of stroke risk and potential interventions." ❋

About the researcher

AHFMR Senior Scholar **Dr. Marc Poulin** is an associate professor in the Faculty of Medicine and the Faculty of Kinesiology at the University of Calgary.

Selected publication

Foster GE, Hanly PJ, Ostrowski M, Poulin MJ. Effects of continuous positive airway pressure on cerebral vascular response to hypoxia in patients with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 2007 Apr 1;175(7):720-725.

Recommended websites

Laboratory of Human Cerebrovascular Physiology
http://www.ucalgary.ca/~poulin

Heart and Stroke Foundation of Canada
http://www.heartandstroke.ca

STRESS

We all know what stress feels like—whether it's caused by situations at work, pressures at school, problems at home, family responsibilities, or rocky interpersonal relationships. But what happens in our bodies when we experience stress? Why are some people more vulnerable to stress than others? And how can we reduce the effects?

■ FOR MUCH OF THE TIME THAT HUMANS HAVE WALKED THIS PLANET, daily stresses were a lot different than they are today. Wild animal attacks, marauding tribes—the kind of stuff that really demands a fight-or-flight response. In cases of physical threat, the human body must be able to switch into high gear. It needs the energy,

The unrelenting triggering of the stress response can make us sick in ways we are only now beginning to identify

speed, and concentration to either stand and fight or hightail it out of there.

Of course, we still need the stress response—for slamming on the brakes to avoid an accident, for focusing our minds as we take a final exam. But it's supposed to turn off once the threat is over. The problem is, physical threats are not the only triggers of the stress response. Situations at work, relationships under pressure, and major life changes can kick the stress response into high gear and keep it going. And that's where we run into difficulties. The unrelenting triggering of the stress response can make us sick in ways we are only now beginning to identify.

"Our understanding of the basic biology of stress just isn't there yet," says Heritage Senior Scholar Dr. Jaideep Bains, a neuroscientist at the University of Calgary's Hotchkiss Brain Institute. "If your car breaks down, a mechanic can fix it—because there's a huge body of knowledge about the parts of a car and how they work together. When your body breaks down in response to stress, the doctor may know the parts, but no one has figured out how they work yet. So there's a big disconnect. Basic research is aimed at figuring out what the parts do."

HOW BRAIN CELLS TALK

Dr. Bains and his lab are focusing on how cells in the brain "talk" to each other. His particular interest is the role of glial cells. Although the human brain is more than half glial cells by volume, these cells were previously thought to do

Dr. Bains investigates how stress alters brain circuitry

little more than hold the brain together so that the neurons (nerve cells) could do the important work of carrying messages. Glial cells were considered to be passive bystanders in the process of neural transmission. Dr. Bains's research has uncovered a rich two-way communication between neurons and glial cells.

By receiving chemical signals, glial cells "listen" to what the neurons have to say. They can also send messages back to neurons by releasing chemical signals. In particular, glial cells release a chemical called ATP that helps neurons communicate with each other more effectively. This role led Dr. Bains to suspect that glial cells might be integral participants in coordinating the stress response.

ELECTRICAL SIGNALS

He is following up on this hunch with experiments recording the electrical signals from neurons and glial cells. The cells he examines are from the hypothalamus, the part of the brain that coordinates the release of hormones during stress—either to activate the stress response or to return the body to its normal balance. Both neurons and glial cells can be stimulated with different patterns of electrical activity to see how transmission changes. Dr. Bains and his team also use an experimental model to investigate how stress alters brain circuitry.

"We're only beginning to scratch the surface in understanding the dynamic interplay between cell groups," says Dr. Bains. "The brain is phenomenally more complex than we thought."

About the researcher

Heritage Senior Scholar **Dr. Jaideep Bains** is an associate professor at the Hotchkiss Brain Institute at the University of Calgary.

Selected publication

Gordon GRJ, Baimoukhametova DV, Hewitt SA, Rajapaksha WRAKJS, Fisher TE, Bains JS. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. *Nature Neuroscience* 2005 Aug;8(8):1078-1086.

Further reading

Sapolsky RM. *Why Zebras Don't Get Ulcers: The Acclaimed Guide to Stress, Stress-Related Diseases, and Coping, 3rd ed.* New York. Henry Holt; 2004.

Stress and mental health

Severe stress experienced in childhood is one of several factors that can put people at risk for depression and post-traumatic stress disorder (PTSD). Extreme adversity, poverty, maltreatment, physical or sexual abuse, the loss of a parent—any one of them can make someone more vulnerable to these disorders. Heritage Scholar Dr. Nick Coupland wants to find out why. A practising psychiatrist and University of Alberta psychiatry professor, Dr. Coupland conducts research on the neurobiology and neuroscience of stress, anxiety, and depressive disorders.

■ One of his research programs was inspired by results from post-mortem studies of people who had suffered from depression. These people had fewer glial cells in the *frontal* part of their brains—the place where emotions are generated and regulated. "This is a very interesting finding, and we've been following this up by developing ways to measure the activity of glial cells in living people."

To do this, Dr. Coupland's team uses *MRI spectroscopy*, a non-invasive technique that measures chemicals in the brain by means of a strong magnetic field. Of particular interest is glutamine, a chemical stored almost entirely in a particular type of glial cells called astrocytes. By measuring glutamine and its concentration relative to other brain chemicals, researchers may be able to determine whether a brain has fewer glial cells than normal.

Dr. Coupland's team will assess brain chemicals in people with depression and PTSD

The team is now recruiting participants for a clinical trial to assess these chemicals in people with depression and PTSD. The trial involves measurement of brain chemicals, and structural imaging of both the grey matter that performs mental activities and the deeper white matter that links those activities across the brain. Participants will also be asked about their past experiences, so that the researchers can try to determine whether different degrees of childhood stress affect the chemical and structural measurements of the brain.

"Our hope is that this research will open up new avenues to treat depression," says Dr. Coupland. "We've known since the 1950s that depression can often be lifted by raising the level of serotonin, one of the main neurotransmitters in the brain. Antidepressant drugs that elevate serotonin are still the first-line treatment for depression. But they don't work for everyone. We need new targets.

"There is a stigma about depression, and a stereotype that people who suffer from depression are weak. Actually, people with depression

Interested in research?
If you suffer from depression or post-traumatic stress disorder, you might be interested in taking part in research aimed at a better understanding of these disorders. Contact Dr. Nick Coupland's research team in Edmonton at 780-492-6024.

are some of the most strong-willed and courageous people I've met. If you've ever experienced depression, you know how much it takes to just keep going. When you hear of the childhood experiences that many people have been through, you can have nothing but admiration for them."

About the researcher *Heritage Scholar* **Dr. Nicholas Coupland** is an associate professor in the Faculty of Medicine and Dentistry (Department of Psychiatry) and director of the Psychopharmacology Research Unit at the University of Alberta.

Selected publication

Coupland NJ, Ogilvie CJ, Hegadoren KM, Seres P, Hanstock CC, Allen PS. Decreased prefrontal myo-inositol in major depressive disorder. *Biological Psychiatry* 2005 June 15;57(12):1526-1534.

Recommended websites

Anxiety Disorders Association of Canada
http://www.anxietycanada.ca/english/index.php

National Center for Posttraumatic Stress Disorder
http://www.ncptsd.va.gov/ncmain/information/

Stress and women

University of Alberta nursing professor Dr. Kathy Hegadoren also studies vulnerability to stress. Her focus is the psychological and biological factors that determine why women are more vulnerable than men to stress disorders.

■ WOMEN EXPERIENCE DEPRESSION AT ROUGHLY TWICE THE RATE THAT MEN DO, and are more vulnerable to PTSD. A number of social and political factors come into play including poverty, social justice, burden of child care, home responsibilities, and working outside the home. Biological factors may also be present as suggested by the fact that the difference in the rate of depression between men and women does not show up until puberty. In addition, women are vulnerable to depression after childbirth and around the time of menopause.

"Given all these factors, it's very difficult to tease out the effects of each one," notes Dr. Hegadoren. "My background as a nurse and my training as a basic scientist have given me the tools to start integrating these pools of knowledge.

"The link between depression and exposure to serious stressors or trauma is very strong. Research on the neurobiology of severe stress has focused on the experiences of combat soldiers, prisoners of war, firefighters, and police. But women's trauma is often around interpersonal relationships. So my research has evolved into recognizing that it's important to start with those experiences and understand their full impact on women's mental and physical health."

Dr. Hegadoren's research covers a wide range of studies on topics that include intimate partner violence against women; pregnancy and birthing experiences of women who were sexually abused in childhood; and decision-making around alcohol use during pregnancy. She collaborates with Dr. Coupland in a study that examines the emergence of stress symptoms, changes in stress hormones, and coping patterns in the early aftermath of mo-

"The link between depression and exposure to serious stressors is very strong"

tor-vehicle accidents. The team hopes to determine what distinguishes people who recover from trauma from those who progress to PTSD or other disorders.

"Preventing and minimizing the potentially adverse effects of prolonged or intense stress on health is a critical challenge," says Dr. Hegadoren. "There is an emerging body of knowledge telling us that, no matter what organ system or disease you look at, there are fundamental gender differences in physiology, pathology, and how symptoms are interpreted and managed. We need to be better at incorporating this knowledge into health-delivery systems—not just for mental health."

About the researcher
Dr. Kathy Hegadoren is an associate professor in the Faculty of Nursing at the University of Alberta and director of the Women's Health Research Unit. She is also Canada Research Chair in Stress-Related Disorders in Women.

Selected publication
Hegadoren KM, Lasiuk GC, Coupland NJ. Posttraumatic stress disorder part III: health effects of interpersonal violence among women. *Perspectives in Psychiatric Care* 2006 Aug;42(3):163-173.

Further reading
Seeman N, Seeman MV. *Psyche in the Lab: Celebrating Brain Science in Canada*. Toronto (ON): Hogrefe; 2006.

Stress and prenatal care

Increased understanding of the links between stress and depression has inspired Heritage Population Health Investigator Dr. Suzanne Tough to follow up with research in her field of maternal and child health. An associate professor in the University of Calgary's Faculty of Medicine, Dr. Tough is also associate director of the Institute of Maternal and Child Health and scientific director of the Alberta Centre for Child, Family and Community Research.

■ "ALTHOUGH WE KNOW THAT STRESS INFLUENCES MENTAL HEALTH, we haven't done a good job of linking this knowledge across the trajectory from conception to birth and into childhood," she says. "We tend to look at maternal depression when the baby is six months old and mom is not doing well. But how did this situation develop? Can we intervene early to reduce the likelihood of depression? This is really important because depression affects a mother's likelihood of breastfeeding and her ability to pay attention to infant cues and to engage visually with her child."

These concerns provided the background to a clinical trial of prenatal care conducted in Calgary

"Reducing stress for moms-to-be will hopefully lead to a better pregnancy and birth experience"

The search led Dr. Tough to a program called Centering Pregnancy, developed by a midwife in the United States, where women receive prenatal care and education in a group setting with women at the same stage of pregnancy. A clinical trial of group prenatal care is under development using these principles, and will begin in Calgary this spring. Dr. Tough hopes to enrol 1,500 women.

"This program is a model of empowerment and social support. Reducing stress and isolation for moms-to-be will hopefully lead to a better pregnancy and birth experience. There are a lot of other ways we could look at improving social support, but this is an exciting start."

in 2005. It investigated three different prenatal-care models to determine the impact of extra prenatal support. The models were: standard clinic care; standard clinic care with nursing support; and standard clinic care with nursing support and home visitation. More than 2,000 women participated in the study, and more than 1,500 of them (77%) completed it.

About 80% of women who had extra nursing support felt they benefited from it; just over 40% of women who saw the home visitor said they benefited. For Dr. Tough, one of the most compelling results was that the women who benefited the most from support were those at highest risk: new Canadians, women with a low family income, and those who faced challenges in getting enough to eat and finding secure housing. However, these were also the women most likely to leave the study.

"The results say to me: We can get high-risk women into care but we can't retain them. I believe there is something about the way we're delivering services that discourages our most vulnerable women from using them. I think our structures and processes are a barrier; they create stress and isolation. We need to find better ways to reduce stress, by providing social support in addition to looking after the medical needs of pregnant women."

About the researcher
Heritage Population Health Investigator
Dr. Suzanne Tough
is an associate professor in the Faculty of Medicine at the University of Calgary. She is also associate director of the Institute of Maternal and Child Health and scientific director of the Alberta Centre for Child, Family and Community Research.

Selected publication

Tough SC, Johnston DW, Siever JE, Jorgenson G, Slocombe L, Lane C, Clarke M. Does supplementary prenatal nursing and home visitation support improve resource use in a universal health care system? A randomized controlled trial in Canada. *Birth* 2006 Sep;33(3):183-194.

Recommended website
Alberta Centre for Child, Family and Community Research
http://www.research4children.com

Reducing stress

As research gives us a clearer picture of the damaging effects of stress, the results raise the question, What can we do about it? Dr. Linda Carlson, a clinical psychologist at Calgary's Tom Baker Cancer Centre and an associate professor in the Faculty of Medicine at the University of Calgary, has been looking for answers. Combining her training in clinical health psychology with a personal interest in meditation and yoga, she takes a behavioural approach to stress reduction.

■ "THINGS HAPPEN IN THE WORLD THAT ARE BEYOND OUR CONTROL. They may or may not be interpreted as stressful; it depends on the person. It's not the traffic jam *per se*, but how we respond to the traffic jam that determines the physical, psychological, and behavioural stress symptoms. So my interest is in changing the way we interpret these events, thereby reducing stress."

To do this, Dr. Carlson uses a well-known program called *mindfulness-based stress reduction*. It was developed by Dr. Jon Kabat-Zinn at the University of Massachusetts. Mindfulness (an intentional, focused awareness) is a way of paying attention in the present moment, non-judgmentally. The eight-week mindfulness program teaches people to direct their attention to their present experience, instead of letting their minds ruminate about the past or race ahead to worry about the future. It emphasizes open acceptance and non-judgment—learning to let go, learning to stop trying to control things that you cannot control.

Dr. Carlson uses a program called mindfulness-based stress reduction

Dr. Carlson emphasizes that mindfulness goes much further than conventional relaxation training. "The program is about an essential way of being in the world. It looks at how people interpret [the situations they're in] and cause their own stress. We use meditation, yoga, and group dialogue aimed at self-reflection and self-knowledge. The benefits include decreases in stress symptoms, an increased ability to relax, reductions in pain levels, and greater energy."

Documenting and evaluating these benefits by means of clinical trials is a major theme in Dr. Carlson's research. She mentions a current study that compares mindfulness to support groups for breast-cancer patients. "Many clinical trials compare mindfulness to no intervention at all. My goal is to do more head-to-head comparisons with active intervention." Another trial evaluates the comparative benefits of mindfulness and acupuncture as means of reducing pain in women receiving palliative radiation therapy for bone cancer.

"It's very powerful to see what a difference learning these techniques can make in people's lives," says Dr. Carlson. "I'd like to see stress-reduction programs integrated in health care and universally available. But this won't happen until we have strong evidence of effectiveness. My mission is to develop this evidence in different ways by investigating biological and psychological mechanisms, and testing mindfulness in different populations. It's the only way this will get into the mainstream." ❋

What is the stress response?

Often called the "fight-or-flight" reaction, the stress response automatically shifts the body into high gear, preparing it for a physical threat. When a threat is perceived, the hypothalamus (located in the lower central part of the brain) signals the adrenal glands (which sit atop the kidneys) to produce more of the hormones adrenalin and cortisol. Results can include the following:

- The heart rate, breathing rate, blood pressure, and metabolism increase.
- The blood vessels open wider to let more blood flow to large muscle groups.
- The pupils dilate to improve vision.
- The brain activates nerve cells to make you more alert and responsive.
- The liver releases some of its stored glucose to increase available energy.
- Sweat cools the body.
- Unnecessary functions like digestion and sexual function shut down to free up blood for other parts.

Edmonton psychiatrist and Heritage researcher Dr. Nick Coupland cautions that, while these physiological reactions to stress are common, there is really no single type of stress response. "In some cases of uncontrollable stress, there may be heart-rate slowing, passive immobility, and shutting off from the environment. Sometimes giving up—not competing—is the best adaptive response, especially if it keeps you from being killed. Personal losses are another important type of stress event that do not manifest themselves in the same way as fight-or-flight." ❋

About the researcher

Dr. Linda Carlson is a clinical psychologist with the Tom Baker Cancer Centre and an associate professor in the Faculty of Medicine at the University of Calgary.

Selected publication

Carlson LE, Speca M. Managing daily and long-term stress. In: Feuerstein M, editor. *Handbook of Cancer Survivorship*. New York: Springer Books; 2007. pp. 339-360 (chap. 19).

Recommended websites

Center for Mindfulness in Medicine, Health Care, and Society
http://www.umassmed.edu/cfm/index.aspx

Calgary Mindfulness-based Stress Reduction Interest Group
http://www.mindfulnesscalgary.ca

Dr. Linda Carlson's website
http://www.ucalgary.ca/~lcarlso

Investing in people

Healthcare workers carry heavy burdens—increasing workloads, staff shortages, and high turnover rates. Dr. Greta Cummings proposes that a new style of leadership and management training may be crucial to improving health care.

FIRST-HAND KNOWLEDGE

"When I started nursing I was in charge of four to five patients at a time," says Dr. Greta Cummings. "As I moved into more senior management positions I was in charge of 30 patients, then 100 patients, and eventually over 200 patients." Now an AHFMR Population Health Investigator, she has parlayed this first-hand experience as a healthcare manager into a career in research and teaching at the University of Alberta.

Dr. Cummings has spent 20 years of her career in various leadership positions, including positions involving planning and policy-making. As a senior administrator, she saw the stresses faced by nurses on a daily basis. "I was working in the hospital system in the nineties, during a time of massive cutbacks. I had to lay off so many nurses, and I wanted to know what that had done to the system—and, in particular, to the nurses who were left behind."

Dr. Cummings saw the stresses faced by nurses on a daily basis.

LEADERSHIP STYLES OF HEALTHCARE MANAGEMENT

Dr. Cummings studies the impact of leadership style on nurse morale. In particular, she examines the effects of *emotionally intelligent leadership*. Emotionally intelligent leaders foster relationships in the workplace and spend time investing in the personal and professional development of their staff. "This style of manager does not view an employee as 'just a worker', but as a person," explains Dr. Cummings. "I was really keen on knowing if nurses who worked for this type of leader fared differently from nurses who worked for other types."

Her systematic reviews of existing literature showed that leadership style played a pivotal role in the lives of nurses. Despite experiencing restructuring, layoffs, and increased patient load, nurses who reported to emotionally intelligent leaders were healthier, less emotionally exhausted, and better able to look after their patients than nurses who worked for performance-focused, commanding leaders. "Managing people by projecting the attitude that 'it's my way or the highway' is much less effective in the long run," says Dr. Cummings.

She also points out that a focus on the bottom line likely wastes more money than it saves. "The attitude of 'let's do it my way because we'll get to the bottom line' probably costs the system a lot in terms of turnover and grievances. If we can engage staff in a meaningful way, we will have fewer organizational problems. In the end it will cost less, and we will have better outcomes."

Although the impact of leadership style has been well documented in other sectors, Dr.

> "An organization's staff is its most important resource."

Cummings's research program is one of the first of its kind to address the effect of leadership styles on the Canadian healthcare system. "Leadership style has farther-reaching implications than job satisfaction," says Dr. Cummings. "It leads to better patient care and retention of nurses; and it will ultimately save the system money. An organization's staff is its most important resource."

PUTTING THEORY INTO PRACTICE

Dr. Cummings is now moving on to explore the question of how best to train effective leaders. "We don't have much research on how to develop leadership in health care. How do we develop young leaders? How can we improve patient outcomes through better leadership? Healthcare workers are burnt out, and there are high rates of absenteeism. We haven't solved the problem yet."

Currently Dr. Cummings is working with the Alberta Cancer Board to implement a program called the Leadership Development Initiative (LDI). "Rather than sending leaders out of the system to receive training—after which they have to bring learned skills back and try to change the workplace culture—we're trying to work within the system," explains Dr. Cummings. The LDI has the potential to change the way nurses and other healthcare professionals train, as well as the way they interact with each other and work together. ❋

About the researcher

Dr. Greta Cummings is an *AHFMR Population Health Investigator* and an assistant professor in the Faculty of Nursing at the University of Alberta. She is also principal investigator for the CLEAR Outcomes Research Program (Connecting Leadership, Education and Research).

Selected Publications

Cummings G, Hayduk L, Estabrooks C. Mitigating the impact of hospital restructuring on nurses: the responsibility of emotionally intelligent leadership. *Nursing Research* 2005 Jan/Feb;54(1):2-12.

On the path to a cure for diabetes

Shaheed Merani, 2007 McLeod Scholarship winner, is looking for ways to improve the Edmonton Protocol for type 1 diabetes patients.

In 1922 Banting, Best, and Collip discovered that injecting diabetes mellitus patients with the hormone insulin could significantly improve their quality of life. Diabetes patients produce high levels of blood glucose (blood sugar); insulin shots help regulate these levels, thereby avoiding serious medical complications. Ever since that initial discovery, researchers have been trying to go beyond managing the disease and actually find a cure. Shaheed Merani, winner of the 2007 Lionel E. McLeod Health Research Scholarship, awarded by AHFMR, is a member of the next generation of these researchers.

The University of Alberta M.D.-Ph.D. student works with AHFMR Scholar Dr. James Shapiro, a surgeon and diabetes researcher. Dr. Shapiro is renowned for his groundbreaking work in islet transplantation as a potential cure for diabetes, a method known worldwide as the Edmonton Protocol. *Islets*

> One of these hormones can trigger higher levels of insulin release

are tiny structures in the pancreas that contain as many as a thousand cells, including—most importantly for diabetics—the beta cell that produces insulin. Instead of transplanting the whole pancreas, which is a very invasive procedure, the Edmonton Protocol involves isolating hundreds of thousands of islets and injecting them into the portal vein of the liver. There the islets establish a new home and begin producing insulin.

During the initial trial in 2000, patients underwent islet transplantation surgery and received a combination of drugs to prevent rejection of the foreign tissue. Amazingly, all of the patients were able to abandon the daily injections of insulin they had needed to regulate their blood sugar. However, the treatment did not prove to be a cure. Five years after surgery the injected islets were producing significantly less insulin, and most patients had to begin insulin injections again. In spite of this setback, the researchers believe that the therapy has tremendous potential, and they continue to work in the area.

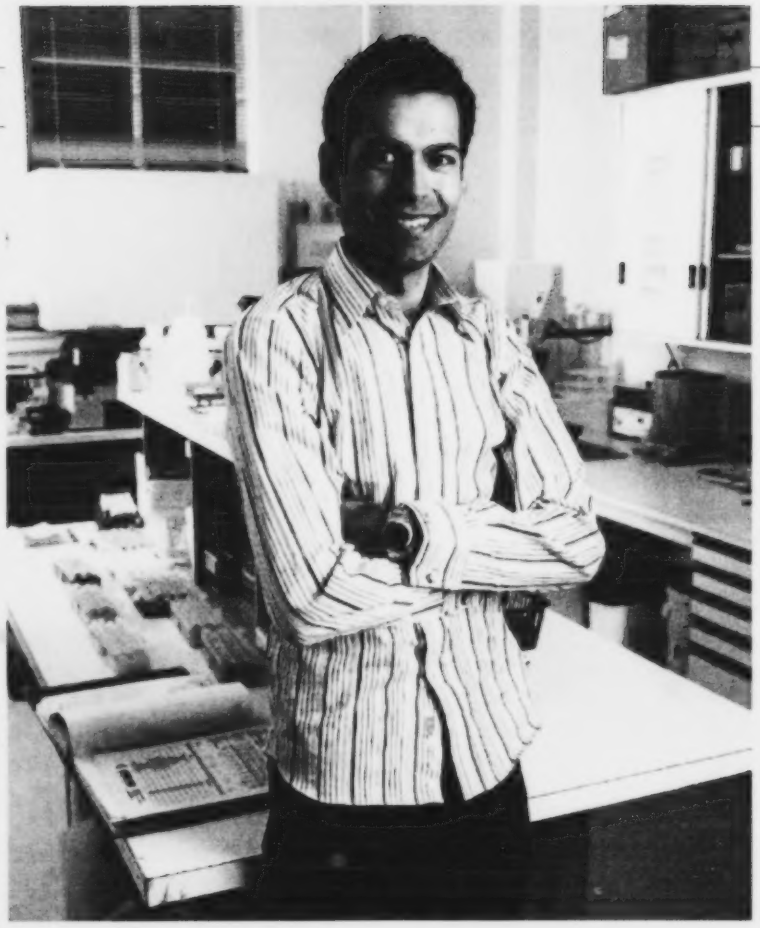
These days Dr. Shapiro's group are taking a two-pronged approach toward making islet transplantation more effective

> Merani is looking forward to getting back to the clinic

in the long term. On the one hand, they research a variety of immunosuppressant drugs to determine how best to prevent the body from rejecting transplanted islets. On the other hand, they also investigate ways to increase islet function after transplantation, in order to extend the life of islets and lengthen the period of time that patients can go without insulin injections.

In Merani's first major research project upon joining the lab, he found that islets become damaged by compression during the isolation procedure. It was a simple but vital finding, and it could improve the clinical methods used to obtain islets for transplantation. Since completing that study, however, Merani has switched gears.

"We're into using various hormonal peptides that may improve the function of the islets themselves, and necessitate fewer islets for transplantation, which is one goal of our work," he explains. One of these hormones can trigger higher levels of insulin release from islets in response to glucose, making it an exciting prospect for the lab.



The same hormone also plays a role in preventing the death of beta cells and increasing the number of islet cells.

While this research is clearly still at the basic-science stage and far from ready for patient care, Merani is optimistic. "It's great to be part of a group that works with the clinical islet transplantation program. Our research can definitely have a direct impact on the work that's done in human patients."

Merani is looking forward to getting back to the clinic himself. He hopes to finish his doctoral work in the next two years, and then return to medical school to decide what specialty to pursue. Meanwhile he is clearly satisfied with his decision to return to his hometown of Edmonton for this part of his training. ❋

About the researcher
Shaheed Merani is an *AHFMR M.D.-Ph.D. student* at the University of Alberta who was recently awarded the AHFMR Lionel E. McLeod Health Research Scholarship.

Selected publication
Merani S, Schur C, Truong W, Knutzen VK, Lakey JRT, Anderson CC, Ricordi C, Shapiro AMJ. Compaction of islets is detrimental to transplant outcome in mice. *Transplantation* 2006 Dec 15;82(11):1472-1476.

AHFMR funding partners

The Alberta Heritage Foundation for Medical Research (AHFMR) has contributed more than $900 million to Alberta's health-research community. The Foundation also relies on the contributions of many partners in building and sustaining health research in this province. To mention just a few, these partners include

- the Government of Alberta and its related ministries and programs;
- federal granting agencies such as the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Canadian Health Services Research Foundation;
- international funding partners like the Wellcome Trust and the National Institutes of Health; and
- non-profit and voluntary funding agencies such as NeuroScience Canada, the Heart and Stroke Foundation, the Canadian Diabetes Association, and the National Cancer Institute of Canada.

Following **up**

Lending Dad a helping hand

Dr. Joyce Magill-Evans (L) and Dr. Margaret Harrison; Dr. Karen Benzies

■ WHEN A COUPLE WELCOME THEIR FIRST BABY INTO THE HOME, life changes dramatically. A number of programs help new mothers cope with the challenges of parenting, but what about new fathers? Researchers Dr. Joyce Magill-Evans and Dr. Margaret Harrison from the University of Alberta, and Dr. Karen Benzies from the University of Calgary, wondered if home visits could help new dads hone their parenting skills. In 2004 they recruited 162 fathers of babies under 5 months of age to participate in their study. Now they are ready to tell Albertans the results.

LEARNING HOW TO PLAY

The fathers received one-on-one home visits from trained professionals who watched them show their infants how to play with a new toy.

The visitors observed the way fathers picked up on their infants' cues, says Dr. Benzies. "Many fathers don't realize the importance of talking to young infants. They're very interested in doing things with their child; but, because babies can't talk, fathers don't feel the need to verbalize to them—which is so important for fostering cognitive growth. We also encouraged fathers to go one step further and use descriptive words to help learning. Instead of saying 'Get it!' they could say 'Get the red rattle with the happy face!'" The visitors gave the fathers feedback and provided written information to reinforce the discussions. In a comparison group, fathers received information on toys from the home visitors, but no feedback on how to interact with their children.

SKILLFUL PARENTING

Follow-up visits when the babies were 8 months old showed that fathers who had received two home visits were more skilled at fostering their children's cognitive development and were more sensitive to infant cues that those in the comparison group. ❋

About the researchers

Dr. Joyce Magill-Evans is a professor in the Department of Occupational Therapy, part of the Faculty of Rehabilitation Medicine at the University of Alberta; and **Dr. Margaret Harrison** is professor emeritus in the Faculty of Nursing. **Dr. Karen Benzies** is an associate professor in the Faculty of Nursing at the University of Calgary. Their study was supported by the *Health Research Fund*, which is administered by AHFMR on behalf of Alberta Health and Wellness.

Recommended websites

National Project Fund on Fathering
http://www.mydad.ca

National Center for Fathering
http://www.fathers.com

Fathers' Forum Online
http://www.fathersforumcom

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